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REVIEW ARTICLE

Gastric cancer: adjuvant chemotherapy versus chemoradiation. A clinical point of view

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Summary

Gastric cancer represents one of the most severe cancers with poor overall survival. Despite the availability of published data on the efficacy of adjuvant treatment, the actual percentage of treated patients remains low. The toxicity of radiotherapy or chemotherapy regimens differ and clinicians need accessible tools in order to better select candidates for adjuvant treatment. In this review, we present published data from clinical trials and cancer registries that might be useful for properly balancing the efficacy and toxicity of adjuvant treatment in gastric cancer patients who underwent surgery with curative intent.

Key words: *gastric, cancer, adjuvant, radiotherapy, chemotherapy*

Introduction

Gastric cancer represents one of the most severe types of malignant tumors. Despite its lowered incidence due to better food preservation techniques, it remains a deadly disease.

In 2018, Globocan reported over 1 million new cases with a mortality of 780000 per year, which places gastric cancer on the fifth place in terms of prevalence and on the third place in terms of cancer-specific deaths [1]. Worldwide, gastric cancer is ranked third in mortality, regardless of national income [2].

As far as society costs are concerned, gastric cancer is one the most expensive diseases in Southern and Central-Eastern Europe, where the socioeconomic impact is estimated at 5.4 and 6.1% of total costs [3]. The estimated negative impact of premature death in cancer patients in Europe was 75 billion euros in 2008 [3].

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The natural history of gastric cancer

Patients with gastric cancer are difficult to diagnose due to their unspecific symptoms. Because they are frequently diagnosed at an advanced clinical stage, only oncological treatments with palliative intent can be administered. With the exception of Japan and Korea, there are currently no guidelines for gastric cancer screening [4]. A recommended screening schedule is not available even for patients with premalignant lesions.

Prognostic factors – a means of better patient selection

A better selection of the patients at risk represents one way of improving gastric cancer results. This can be achieved through the panel of prognostic factors presented below.

Clinical symptoms

The clinical symptoms are not very specific and therefore unable to signal the presence of neoplasia. Weight loss, dysphagia and a palpable epigastric mass, which were reported by patients late in the natural history of the disease, usually indicate an advanced disease stage with a high risk of cancer-related death [4]. In a prospective clinical study of 1852 consecutive cases of gastric cancer, Kapoor et al showed that weight loss and dysphagia represent predictive factors for cancer but their value is very limited [5]. Patients with no alarm symptoms seem to have a better survival and a lower stage of the disease [6]. On the other hand, an abdominal palpable mass seems to be more closely associated with poor survival probability than all the other alarm symptoms, with a median survival of only 10 months [7]. Less common, this clinical presentation could be misinterpreted as pancreatic cancer [8].

Overall, the positive predictive value of symptoms for gastric cancer is below 10 %, which makes the clinical use of alarm symptoms very limited [9].

TNM stage

The general prognosis is related to the clinical evolution and stage, which are both taken into account when establishing the clinical management plan for gastric cancer patients. Locoregional or metastatic spread of the disease have different life expectancies. Overall survival (OS) at 5 years reached 68.1% in patients with local disease, but it diminished to 30.6% in case of lymph node involvement and to 5.2% in a metastatic setting [10]. The OS at 5 years was less than 50% in patients with a clinical stage higher than II [11].

The general trend in gastric cancer survival is positive as the 5-year overall survival increased from 15% in 1975 to approximately 31% at present [10].

T stage

Depth of tumor invasion seemed to be a prognostic factor for OS in a published retrospective analysis of 1715 patients with curative resection for gastric cancer [11].

T stage has been demonstrated to be linked with the risk of local relapse compared with N stage, which is more related with distant metastasis [12].

A more advanced depth of tumor invasion increases the risk of lymphovascular invasion or lymph node micrometastasis [13]. This is why the evaluation of gastric cancer patients with more advanced T stages (T3 and T4) requires the harvesting of a higher number of lymph nodes (at least 18), which seems to be significantly linked with improved OS [14].

Even in a very early stage (T1), the invasion of muscularis mucosa produced lymph node metastasis in 4% of the cases [15]. In the case of tumors larger than 2 cm invading more than two portions of the stomach, 20.5% of the patients had already developed peritoneal metastasis [16].

Adjuvant treatment such as chemotherapy (CT) or chemotherapy plus radiotherapy (CTRT) should be proposed to patients in stages higher than T2 depending on the postoperative histological results, performance status and prognostic factors.

N stage

Lymphatic invasion is one of the most powerful prognostic factors in gastric cancer. Even in early gastric cancer limited to the mucosa, the approximately 3% estimated risk of positive lymph nodes (depending on tumor size, presence of ulceration, grade of differentiation, perineural and lymphatic invasion) is not to be neglected [17].

Lymphadenectomy – curative or staging purpose?

The number of lymph nodes that should be removed during surgery continues to be a subject of debate. For the time being, the 8th edition of the UICC/AJCC staging system for gastric cancer, similarly to the 7th edition, recommends the removal of at least 16 lymph nodes for correct lymph node assessment, as shown in a systematic review conducted by Coburn et al [14].

Is lymphadenectomy simply a pathological staging method or should it be the aim of curative intervention?

A meta-analysis by Mocellin and Nitti comparing D1, D2 and D3 resections in more than 2500

patients showed that D2 offers better disease-specific survival (DSS) but no OS and disease-free survival (DFS) advantage compared with D1, while no differences between D2 and D3 in terms of DSS, DFS and OS were found [18].

An analysis of "real life patients" using the US Surveillance, Epidemiology, and End Results database investigated the number of lymph nodes removed by stage subgroup (T1/2N0, T1/2N1, T3N0, and T3N1) [19]. The OS results showed that every 10 lymph nodes removed led to statistically significant survival advantage for each analyzed stage, which ranged between 5 and 11% depending on the final clinical stage [19].

It must be underlined that a low number of nodes was involved in the stages included in the analysis, which facilitated the surgical effort. Not least, the surgeon must be aware that in 3.9% of gastric cancer patients who are resectable a skip metastasis could be met [20].

N3 patients

A previous TNM staging classified stage N3 (more than 15 positive lymph nodes) as stage 4 without visceral metastasis. The OS in a large series of 422 N3 gastric cancer patients ranged between 10.5% and 0%, depending on T stage (T1-3 and T4, respectively) [21]. T4N3 patients had slightly lower survival than those with M1 (visceral metastasis).

Distant metastasis rather than locoregional relapse is a more frequent cause of death in this category of patients. *The addition of radiotherapy to chemotherapy does not improve the general results for N3 stage*, as shown in a retrospective analysis of 276 patients who underwent D2 and R0 resection plus adjuvant chemotherapy or radiochemotherapy [22]. In N1-2 stages only the 3-year DFS and local control seem to be higher, but not the OS. Even the addition of anthracycline to a chemotherapeutic regimen seemed to not improve OS [23].

Lymph Node Ratio (LNR)

LNR (the ratio of involved lymph nodes to the total number of removed lymph nodes) could be an important tool for better selection of adjuvant treatment in patients with optimal surgical resection (D2) according to recently published data suggesting that LNR > 25% treated by chemotherapy in association with radiotherapy had better DFS compared with patients treated by adjuvant chemotherapy alone [22]. LNR could also be used as a prognostic factor even in patients with less than 15 lymph nodes removed (suboptimal resection according to the UICC/AJCC), as demonstrated on a large cohort of patients (>2500) in China [25].

Moreover, in a cohort of 3284 patients, LNR showed to be a better predictor of OS than N stage [26]. A lower LNR (less than 6%) from a higher number of lymph nodes removed was found to statistically correlate with better OS in patients with pN2, pN3a, and pN3b stages [26]. LNR could discriminate between subgroups with different chances of survival [27].

Adjuvant treatment in the form of chemotherapy associated with radiotherapy could be chosen in patients with high LNR, who have higher survival improvement chances.

N negative

In a retrospective study conducted by Jin et al, 39% of 805 patients with resected gastric cancer had stage N0. As the most powerful negative prognostic factor was absent in this cohort of patients, the risk of relapse was statistically correlated with stage T3, the presence of lympho-vascular invasion invasion and signet cell histology [28].

These negative factors were also analyzed by other researchers, as detailed below.

In a retrospective analysis of 1971 patients with early stage gastric cancer (IB), Wang et al found that T1N1M0 patients had a worse survival than T2N0M0 patients, especially when surgical resection was suboptimal (less than 15 lymph nodes removed) [27].

With regard to adjuvant treatment, no difference between chemotherapy and radiochemotherapy was highlighted for T1N1M0 versus T2N0M0 [29].

Histological type

In a series of 410 patients with gastric cancer treated with neoadjuvant chemotherapy before curative surgery, the intestinal histological subtype seemed to be a predictive and prognostic factor for OS [30]. The intestinal subtype of gastric cancer had a better response to the standard perioperative chemotherapy regimen (FLOT) in terms of pathological complete response as 85% of the good responders had this histology [31]. The efficacy of CTRT administration in the adjuvant setting was confirmed 10 years after the McDonald et al trial, with the exception of diffuse type histology [29].

Moreover, the same intestinal subtype could be related to a higher probability of being associated with HER2-positive gastric tumors, as shown by Wang et al meta-analysis including 10 studies on 1529 patients between 2012 and 2017 [33].

HER positivity was not correlated with T stage or lymphovascular invasion, although some correlations with the grade of malignancy and male

gender were established. In the ToGA trial, the intestinal subtype of gastric cancer was associated with HER2 overexpression in 32.2% of the cases compared with 6.1% for the diffuse subtype [34]. Breast cancer clinical experience showed that HER overexpression is associated with tumor aggressiveness and lower OS [35].

In the adjuvant setting, the importance of HER overexpression for selecting the intensity of adjuvant treatment has not been established yet.

FLOT could be the preferred chemotherapy regimen for the intestinal type of gastric cancer while radiotherapy could be less effective for the diffuse subtype.

Grade of malignancy / differentiation

In a cohort of 3090 patients treated for gastric cancer, a high grade of malignancy was statistically significantly linked to more advanced disease (T3-4 stage) and more lymph node involvement, therefore the presence of this prognostic factor should be crucial for the administration of an adjuvant treatment [36]. A multivariate analysis of 3039 patients who underwent D2 surgery between 2008 and 2015 showed that, after matching age, T, N stage and tumor size, the results no longer supported the prognostic role of the grade of malignancy in terms of OS (without statistical significance) [36].

Although, according to the available data, the grade of malignancy might not contribute significantly to the selection of CT or CTRT as adjuvant treatment in resected gastric cancer patients, it remains a prognostic factor in favor of adjuvant treatment administration.

Lymphatic or vascular invasion (LVI)

In a retrospective series of resected patients, LVI was found in 44.3% of them [13]. The depth of tumor invasion and lymph node invasion (macro or micrometastases) are statistically linked to LVI positivity.

LVI also increased the risk of positive resection margins in patients with curative resection [37]. *In patients with N0, the presence of LVI should add chemoradiotherapy to the treatment strategy* since LVI correlated with decreased OS in a retrospective analysis of 12504 patients [38].

Positive resection margins (R1)

Data from the two large databases – Lee et al from Korea (1788 patients) [39] and Postlewait and Maithel from the USA (965 patients) [40] underline that the main goal of gastric cancer surgery is to obtain tumor-free resection margins. The length of resection margins does not seem to influence recurrence and survival in more advanced gastric cancer stages (higher than II) [39,40]. R1 resection could be a factor in favor of locoregional and distant relapse [40]. Surgical re-resection could improve prognosis and should only be taken into account in patients with less than 5 positive lymph nodes but it is definitely not indicated in those with N3 disease [40].

Advanced T and N stage, lymphovascular invasion and a high degree of malignancy are factors that could increase the risk of positive resection margins [37].

Data collected from a US National Database showed that OS was better in patients with R1 resection treated with adjuvant radiochemotherapy compared to chemotherapy alone [37].

The Dutch clinical trial conducted by Dikken et al on 91 patients treated with adjuvant radiochemotherapy compared with a historical group of 694 patients randomized between D1 and D2 resection, *supports the role of adjuvant chemoradiation treatment, which improved general survival and the local relapse rate* (2% versus 8% but statistically significant only for D1 resection) in patients with positive resection margins [41].

Tumor markers

Traditional tumor markers are usually used only for monitoring oncological treatment as parts of a complicated puzzle where each component such as imaging, biochemical status, clinical status, tumor markers, nutrition and so on are weighed in order to take the most appropriate decision regarding the possible use of oncological treatment. The diagnostic use of tumor markers is not recognized by well-known international guidelines, although published data suggest their prognostic and predictive role.

In 587 early gastric cancer patients monitored by multiple tumor markers, only CA 19-9 seemed to be statistically significantly linked to the risk of lymph node metastasis [42]. A meta-analysis of 38 clinical trials including more than 11400 patients confirmed that serum levels of CA 19-9 are statistically significantly capable of discriminating between the TNM stage of the disease (III-IV versus I-II), the T stage (T3-4 versus T1-2), lymph node invasion versus N0, presence or absence of vascular invasion [43].

Moreover, a high level of CA 19-9 could predict reduced OS, DFS and DSS [39]. In another study, the early decrease of CA 19-9 (4 weeks after the surgical intervention) was found to be statistically significantly linked to better OS and DFS in a

population of 259 advanced gastric cancer patients (N3 stage) [44].

CA 72-4 is considered more specific and sensitive for gastric cancer [45]. A published meta-analysis, which included 33 clinical trials and 2390 patients, showed that CA 72-4 is the most correlative marker for gastric cancer, with a sensitivity of 50% and an accuracy of 77% [45].

The role of CEA in gastric cancer diagnosis was studied on 4157 subjects (2288 patients with gastric cancer and 1869 patients with benign gastric pathology) [46]. High levels of serum tumor markers correlated with advanced disease stages.

Perineural invasion (PNI)

A published meta-analysis showed the independent prognostic role of perineural invasion in terms of OS and DFS independently of T stage, N stage or tumor size [47]. The median rate of positivity in more than 30000 patients with curatively resected gastric cancer was around 41% [47]. *The presence of PNI should indicate the need for adjuvant treatment in the form of chemotherapy associated with radiotherapy.*

Standard adjuvant treatment

1. Timing of adjuvant treatment in gastric cancer patients

Traditionally, adjuvant treatment was initiated 6-8 weeks after surgery. Greenleaf et al investigated the impact of timing of adjuvant chemotherapy on OS in 7942 resected gastric cancer patients [48]. The groups were as follows: no chemotherapy, less than 8 weeks after surgery, between 8 and 12 weeks and more than 12 weeks after resection. In multivariate analysis, the administration of adjuvant chemotherapy at any time seemed to be superior in terms of OS over surgery alone, with a 27-29% reduction in death rate [48]. Chemotherapy administration, especially in more advanced stages (2 and 3), led to superior OS in each group of patients compared to controls, although no differences were proven as far as the timing of chemotherapy administration was concerned – same OS for early compared with delayed chemotherapy. A retrospective analysis on 266 patients done by Qu et al showed that starting chemotherapy earlier than 45 days could improve OS [49].

Therefore, CT should be administered whenever possible, regardless of its traditional timing after surgery.

Regarding CTRT, a meta-analysis of 13 randomized clinical trials including nearly 3000 patients *did not find any difference between neoadjuvant and adjuvant chemoradiotherapy* [49].

2. Chemotherapy

Older clinical trials investigated the potential role of adjuvant chemotherapy in resected gastric cancer. Inadequate numbers of patients and suboptimal chemotherapy regimens (in today's view) could explain the lack of statistically significant results. Meta-analyses were the first to confirm the positive influence of adjuvant chemotherapy in terms of OS. Table 1 summarizes the most important meta-analyses published to date [50-56].

The most recent results of a meta-analysis conducted by Cao et al on 8580 patients with resected gastric cancer, with or without chemotherapy in the adjuvant setting showed an almost 7% OS advantage at 5 years [57]. Adjuvant chemotherapy seemed to decrease locoregional relapse rates by diminishing lymph node, local and peritoneal re-

Table 1. Meta-analysis of adjuvant chemotherapy in resected gastric cancer

Author	*No. of trials*	*Year of publication*	*No. of patients*	*P value OS*	*Adj CT > observation*
Hu et al. [51]	14	2002	4543	0.0008	Yes
Panzini et al. [52]	17	2002	3118	0.005	Yes
Mari et al. [53]	20	2000	3658	0.001	Yes
Sun et al. [54]	12	2009	3809	0.001	Yes
Zhao et al. [55]	15	2008	3212	0.001	Yes
Liu et al. [56]	23	2008	4919	0.001	Yes
Cao et al. [57]	29	2014	8580	DFS RFS	Yes
Paoletti et al. [58]	31	2010	6390	0.001	Yes

OS: overall survival, DFS: disease-free survival, RFS: relapse-free survival, CT: chemotherapy
*RFS lower recurrence rate (RR: 0.79, 95% CI: 0.74-0.84)

currence [57]. This is a better result for adjuvant chemotherapy compared to the previous meta-analysis, which estimated a lower benefit - 25 patients treated in order to save one. Concerning the type of chemotherapy needed to be used, probably an oxaliplatin-based regimen, should be taken into account; the role of anthracyclines in gastric cancer is contested today despite the fact that some meta-analyses prove a positive effect [58].

In a retrospective analysis of 341 patients Gunaldi et al showed no benefit by adding taxane to classic 5FU and oxaliplatin combination for aged patients (over 65 years) [59]. Oxaliplatin itself could be challenging to be administered due to frequent hypersensitivity reactions on a chronic administratiosn [60].

Furthermore, new data from phase III randomized trials such as ACTS-GC [56] and CLASSIC [62] showed that adjuvant chemotherapy led to a significant OS advantage (10% benefit on average compared with surgery alone).

Moreover, the ESMO guidelines recommend perioperative chemotherapy as the preferred strategy for resectable gastric cancer [63]. Recently published studies demonstrated that adjuvant treatment has an important role in the general management of a case, especially in patients with positive ypN or more than 50% vital tumor cells after neoadjuvant chemotherapy [64]. A meta-analysis published by Hu et al revealed that neoadjuvant sequence of perioperative chemotherapy seemed to be superior in terms of OS at 1.3 and 5 years intervals than surgery alone or surgery followed by adjuvant chemotherapy [65].

It is worth mentioning that the role of adjuvant chemotherapy in elderly patients (>65 years) was investigated in a meta-analysis of 512 subjects published by Chang et al. Adjuvant chemotherapy was not associated with OS advantage despite a statistically significant improvement in the relapse-free survival [66]. The potential benefit of adjuvant chemotherapy could not be denied in these patients, although it might remain small and require the assessment of adverse events related to the chosen chemotherapy regimen.

Target therapy – targeting the EGFR, HER or angiogenesis pathways are not recommended in the adjuvant setting for the time being [63,67].

3. The association of radiotherapy and chemotherapy (CTRT)

Standards of treatment in the adjuvant setting

The association of chemotherapy and radiotherapy after the surgical resection of gastric cancer represents a standard of treatment as the Macdonald trial and the Korean observational study proved the benefit of adjuvant chemoradiation in terms of OS and DFS [68,69]. The positive results of the Macdonald trial in terms of OS were confirmed 10 years after initial data collection in *all categories of patients* except in those with the diffuse histological type [32]. In the Korean study, which included 544 gastric cancer patients who underwent D2 resection and adjuvant chemoradiotherapy (CTRT), survival benefit was obtained even in patients with D2 surgical resection, with a 20% reduction in the death rate and a statistical DFS advantage in favor of CTRT administration for stages II, IIIA, IIIB and IV [69].

N ratio

The ARTIST phase III trial failed to demonstrate a survival advantage for CTRT in patients who underwent D2 resection, although a DFS advantage was highlighted in those with positive nodes [70]. Moreover, a LNR>25% seems to be predictive in patients who benefit the most from CTRT compared to CT alone in terms of OS [70]. These results are conflicting with the Dutch trial [41].

A meta-analysis of 3 randomized controlled trials including 895 patients who underwent D2 resection found that CTRT had a beneficial role in improving locoregional recurrence-free survival and DFS but not OS and distant metastasis recurrence-free survival [71].

CTRT for D1 versus D2 resection

In patients requiring extensive surgical effort (a minimum of 25 lymph nodes harvested during D2 resection) [72]), the results of adjuvant chemoradiotherapy are not in favor of adjuvant treatment due to the fact that OS is statistically not different between arms. In patients with R1 resection, the administration of combined adjuvant treatment is associated with OS advantage and fewer local relapses [40], but only in patients with less than 5 positive lymph nodes, as already mentioned [39].
A retrospective analysis of the Surveillance, Epidemiology and End Results database, which included 11630 patients with gastric cancer between 1990 and 2003, confirmed the role of adjuvant radiation therapy in improving the OS rate [73].

In patients with positive nodes, extensive surgery could help the efficacy of radiotherapy if more than 15 lymph nodes are removed in N1 and N2 disease. In N3 stage patients, the surgical effort is even more aggressive since more than 30 lymph nodes need to be removed [73].

Ohri et al meta-analysis did not find any subgroup of patients with resected gastric cancer who did not benefit from adjuvant CTRT [50].

4. CT versus CTRT

The ESMO guidelines suggest that patients treated with perioperative chemotherapy should not receive adjuvant CTRT [63].

The CRITICS trial compared CTRT versus CT alone after neoadjuvant chemotherapy in 788 patients and found that adjuvant CTRT did not yield an OS advantage [74].

Data from the ARTIST trial suggest that CTRT could have a positive effect compared with CT alone in patients with LNR>25% [69].

A retrospective analysis of the California Cancer Registry including 2146 patients with stages from IB to III showed that those treated by CTRT had the longest OS (52 months) followed by perioperative chemotherapy (33 months) and observation (25 months), based on statistically significant results (p=0.015). Patients with negative nodes and signet ring histology seem to benefit most from CTRT [75]. The same authors published another retrospective analysis of 1493 node-positive patients with stages IB-III and found a statistically significant advantage in OS for patients with LNR>10% who underwent combined treatment compared to chemotherapy alone [64]. We must underline that over 40% of the patients had suboptimal lymph node resection (less than 15) [70].

Another retrospective analysis of the US National Cancer Registry (1998-2006) on 3008 patients who received adjuvant CTRT or CT demonstrated that CTRT led to superior median OS in comparison with CT (36.1 vs 28.9 m; p<0.0001) in N-positive patients, regardless of TNM stage or adequacy of lymph node staging [76]. This benefit was not found in N0 patients.

Dai et al published a meta-analysis which included 1171 patients from 6 randomized trials and showed statistically significant better 5-year DFS and locoregional recurrence rate (LRRR) in patients who underwent CTRT compared with CT alone [77]. A meta-analysis of 4 randomized controlled trials including 960 patients with R0 resection and D2 surgery showed the benefit of CTRT compared with CT alone in terms of locoregional recurrence rate and DFS, but not in terms of OS [78].

Another meta-analysis included 15 randomized clinical trials totaling 3347 patients who underwent surgery and adjuvant treatment in the form of CTRT, chemotherapy or radiotherapy alone. Only 923 patients (27.57%) were included in clinical trials that directly compared adjuvant CTRT with chemotherapy while 2050 patients were not compared with an adjuvant arm [78]. No 5-year OS or DFS benefits were observed in the adjuvant CTRT arm compared with chemotherapy alone, even after stratification for well-known prognostic factors. 811 (24.23%) patients received suboptimal doses of irradiation (30-37 Gy), which could impair the statistical significance. The meta-analysis of Wang et al on 15 randomised controlled trials which included 3347 patients did not find a 5-year OS statistically significant benefit for CTRT over chemotherapy alone in patients with gastric cancer [79].

Ohri et al meta-analysis which investigated the role of adjuvant CTRT in gastric cancer patients found no advantage for CTRT over CT in terms of OS, despite a tendency for statistical significance (p=0.08), but an advantage in terms of DFS in favor of CRT [46]. This advantage was more obviously seen in patients with D0 resection while in those with D1 and D2, the differences were not statistically significant (for D1 p=0.056).

Predictive factors (clinical, histological and molecular)

The US Gastric Cancer Collaborative database analyzed 719 patients who underwent curative resection for gastric cancer, out of which 59.7% had lymph nodes metastasis, and showed that 45.2 % of patients were treated by surgery alone, 35.2% received radiotherapy in association with chemotherapy and 19.6% chemotherapy alone [76].

A positive node ratio was defined (0, 0.01-0.10, 0.10-0.25, >0.25). Patients who received CTRT had a statistically significant survival advantage over patients who underwent chemotherapy alone but only if the lymph node ratio was higher than 0.25 [80]. A positive node ratio >0.25 seems to be a highly predictive and prognostic factor in favor of adjuvant CTRT compared with chemotherapy alone, regardless of lymphadenectomy extent (D2 or D3 versus D0, D1). In patients with suboptimal surgery (D0) the advantage in OS offered by the association of radiotherapy and chemotherapy underlines that the combined treatment is more appropriate instead of chemotherapy alone, regardless of the positive node ratio [80].

Patients aged over 65 years seem to be less frequently selected for adjuvant treatment, irrespective of its form [73]. Pathological T3 or T4 stage, presence of LVI and a high grade of malignancy were associated with the lowest OS. A recently published article showed that younger patients (less than 40 years) with gastric cancer compared with older patients had the same OS [81].

Conclusions

The possible options for resected gastric cancer patients include:

Chemoradiotherapy:
- Postoperatively, if NO preoperative radiochemotherapy was administered, especially in locally advanced esophagogastric junction (EGJ) adenocarcinoma.
- T3/T4 or node-positive (except for LN ratio >25%, N3 or D2 resection, poorly cohesive type).
- T2 + 1 of the following : LVPn+, G3, < 50 of age, < D2 resection.
- R1 resection especially if N stage is <2 and there are less than 5 positive lymph nodes.

Chemotherapy:
- Perioperative or adjuvant for stage ≥IB.

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Conflict of interests

The authors declare no conflict of interests.

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